REMARKS

Entry of the foregoing, reexamination, and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

As correctly stated in the Official Action, Claims 10-20, 25-31, 79, 80, 82, 83, 85-92, 94, 95, 97, 98, 100-110, and 112-123 are pending in the present application. Claims 10-20, 25-31, 86, 100, and 112 stand withdrawn from consideration. Claims 79, 80, 82, 83, 85, 87-92, 94, 95, 101-110, and 113-123 stand rejected.

By the present amendment, Claims 79, 80, 82, 83, 85, 87-92, 94, 95, 97, 98, 101-104, 106, 108-110, 112-116, and 119-123 have been canceled, without prejudice to or disclaimer of the subject matter contained therein. Applicants expressly reserve the right to file a continuation or divisional application on any subject matter canceled by way of the present amendment. Claim 89 has been have been amended to incorporate Claims 79 (with the deletion of "essentially" and characteristics related to stimulation of immunity), 86, and 88. Claim 105 has been amended to incorporate Claims 91 (with the deletion of "essentially" and characteristics related to stimulation of immunity), 100, and 104. Claim 107 has been amended to incorporate Claims 101, 100, and 104. Claim 117 has been amended to incorporate Claims 108 (with the deletion of "essentially" and characteristics related to stimulation of immunity), 112, and 116. Claim 118 has been amended to incorporate Claims 113, 112, and 116. New Claims 124-128 correspond to previous Claims 80, 82, 83, 85, and 87, respectively. New Claims 129-134 correspond to previous Claims 92, 94, 95, 97, 98, and 103, respectively. New Claim 135 corresponds to previous Claim 102. New Claims 136-138

correspond to previous Claims 109, 110, and 115, respectively. New Claim 139 corresponds to previous Claim 114. No new matter has been added.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 79, 80, 82, 83, 85, 87-92, 94, 95, 97, 98, 101-110, and 115-19 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Examiner asserts that the meaning of "consisting essentially of" is unclear. Claims 79, 80, 82, 83, 85, 87, 88, 90, 91, 92, 94, 95, 97, 98, 101-104, 106, 108-110, 115, 116, and 119 have been canceled by the present amendment, thereby mooting this rejection as it applies to these claims. Without conceding to the merits of this rejection, and solely in an effort to expedite prosecution, the wording of independent method Claims 89, 105, 107, 117, and 118, and newly dependent claims thereof, has been amended to delete the recitation of "to stimulate specific immunity in the absence of aspecific immunity" and "consisting essentially of" has been replaced with "consisting of." Withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 79, 80, 82, 83, 85, 87-90, 121, 122, and 123 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description. Claims 79, 80, 82, 83, 85, 87, 88, 90, and 121-123 have been canceled by the present amendment, thereby mooting this rejection as it applies to these claims. Without conceding to the merits of this rejection, and solely in an effort to expedite prosecution, the wording of independent method Claims 89, and newly dependent claims thereof, has been amended to delete the recitation of "to stimulate specific immunity in the absence of

aspecific immunity" and "consisting essentially of" has been replaced with "consisting of." Withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 102

Claims 79 and 87-90 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Stanley et al. (U.S.P.N. 6,096,869). Claims 79, 87, 88, and 90 have been canceled by the present amendment, thereby mooting this rejection as it applies to these claims. This rejection, to the extent that it may apply to Claim 89, as amended, is respectfully traversed.

Independent Claim 89 recites a method for the treatment or prevention of dysplasia or cancer of the neck of the uterus caused by a papillomavirus, utilizing a pharmaceutical composition **consisting of** certain papillomavirus polypeptides and a pharmaceutical carrier. Applicants respectfully submit that Stanley et al. do not disclose or suggest a method for treating papillomavirus-induced tumors using a composition consisting of E6, E7, L1, and L2 polypeptides and an appropriate pharmaceutical carrier as recited in amended Claim 89. Rather, Stanley et al. explicitly disclose that IL-12 is critical to provide anti-tumor activity and can be used in conjunction with one or more HPV polypeptides to enhance the IL-12-mediated therapeutic benefit. Accordingly, Stanley et al. cannot anticipate the presently claimed invention. Withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 80, 82, 83, and 85 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Stanley et al. in further view of Crook et al. (*Cell* 67:547-556 (1991)) and Munger et al. (*EMBO J.* 8:4099-4105 (1989)). The Examiner asserts

that one of ordinary skill would have been motivated to incorporate the specific deletions taught by Munger et al. and Crook et al. to significantly decrease or eliminate binding of the HPV-16 E6 and E7 polypeptides to the p53 and retinoblastoma tumor suppressor gene products, respectively. By the present amendment, Claims 80, 82, 83, and 85 have been canceled, thereby mooting this rejection as it applies to these claims. This rejection, to the extent that it may apply to new Claims 124-127 based upon these canceled claims, is respectfully traversed.

As discussed above, Stanley et al. do not disclose or suggest a method for treating papillomavirus-induced tumors using a composition consisting of E6, E7, L1, and L2 polypeptides and an appropriate pharmaceutical carrier as recited in amended Claim 89, from which new Claims 124-127 depend. Rather, Stanley et al. explicitly disclose that IL-12 is critical to provide anti-tumor activity and can be used in conjunction with one or more HPV polypeptides to enhance the IL-12-mediated therapeutic benefit. Neither the Crook et al., nor the Munger et al. references remedy this deficiency of Stanley et al. Accordingly, none of the cited references, either alone or in combination, render the presently claimed invention obvious.

In light of the non-obviousness of independent Claim 89, Applicants respectfully submit that dependent Claims 124-127, which recite the use of non-oncogenic variants of HPV E6 and E7 polypeptides also are non-obvious. Withdrawal of this rejection is respectfully requested.

Claim 121 stands rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Lowy et al. (WO 96/11274) and Galloway (*Infect. Agents & Disease* 3:187-193 (1994)). By the present amendment, Claim 121 has been

canceled, thereby mooting this rejection. This rejection, to the extent that it may apply to newly amended independent Claim 89, is respectfully traversed.

Lowy et al. disclose a method of preventing or treating papillomavirus infection and papillomavirus-induced lesions relying on the use of chimeric virus-like particles (VLP). These chimeric VLP are composed of self-assembled L1 polypeptide and a fusion product between L2 and an early papillomavirus polypeptide. The incorporation of the early polypeptide into the L2 polypeptide leads to the expression of the early polypeptide as a fusion product with the L2 polypeptide resulting in the presentation of the early epitopes at the surface of the VLP. Chimeric VLPs are produced in vitro after infection of Sf9 insect cells with a baculovirus vector co-expressing the L2/E7 fusion gene and the wild-type L1 gene. Rabbits inoculated with such chimeric VLPs produce antibodies that recognize the VLP-exposed E7 polypeptide. Thus, Lowy et al. rely on the use of chimeric L1, L2, and E7 papillomavirus polypeptides assembled in VLPs and disclose the presentation of the early polypeptide E7 at the surface of the VLPs, to be amenable to the immune effector cells and achieve therapeutic benefit.

It is well-known in the art that the production of antibodies involves humoral immunity and that efficient anti-tumoral responses require cell-mediated immunity. In light of this consideration, it should be emphasized that Lowy et al. fail to provide any experimental data that could support effective therapeutic immunoprotection of the chimeric VLPs against HPV-induced tumors. Lowy et al. actually demonstrate that the chimeric L2-E7 fusion become incorporated into the L1-based VLPs. The E7 moiety is indeed presented at the VLP surface because rabbits inoculated with such chimeric VLPs produce anti-E7 antibodies. However, apart from detecting neutralized anti-E7 antibodies in immunized animals (humoral immunity) and

demonstrating prophylactic protection against subsequent papillomavirus infection, Lowy et al. fail to demonstrate any therapeutic protection provided by the chimeric VLP particles presenting E7 at their surface. Upon review of the Lowy et al. publication, it is apparent that Examples 10-13 constitute paper examples describing the kind of experimental procedures that could be used to administer the chimeric VLPs to an animal and to evaluate a possible anti-tumoral response. ("Animals are immunized with, e.g., L2-E7 chimeric VLPs and tested for growth of inoculated tumorigenic cells that express e.g., E7"). However, Lowy et al. do not provide any experimental data that support the capacity of these chimeric VLPs to prevent tumor development and treat papillomavirus-induced cancers with any reasonable expectation of success. Therefore, these "prophetic" examples do not enable a method as claimed in Claim 89.

Galloway does not remedy the deficiencies of Lowy et al. with respect to the presently claimed method. Galloway reviews various preclinical studies that have been performed with either late papillomavirus polypeptides recombinantly produced as fusion proteins (p. 190, second column) or individual early papillomavirus polypeptide (p. 191, from the second sentence to the end of the first paragraph of the first column). There is no motivation in Galloway to treat papillomavirus-induced cancers using a mixture of early E6 and E7 and late L1 and L2 polypeptides, and especially a mixture of non-fused papillomavirus polypeptides.

In contrast to Lowy and Galloway, the method of the presently claimed invention excludes the use of fused early and late polypeptides. The claims have been amended to emphasize this feature, thereby distinguishing the present claims from Lowy et al. and Galloway. The present application provides experimental data illustrating that administration of a composition comprising E6, E7, L1 and L2

polypeptides produced independently (*i.e.*, non-fused) leads to a clear anti-tumoral activity in both therapeutic and prophylactic animal models.

Based on the disclosures of both Lowy et al. and Galloway that early polypeptides should be fused to a late (*e.g.*, L2) polypeptide to be efficiently presented to the host's immune system, one skilled in the art would not be motivated to utilize non-fused papillomavirus early and late polypeptides. In marked contrast, the inventors of the present invention discovered that the non-fused status is more likely to preserve the tridimensional structure of each HPV polypeptide component, and thus, its natural presentation to the immune system. For at least this reason, the non-fused status of the HPV polypeptides used in the method of the presently claimed invention can be advantageous in terms of immunity, and thus, therapeutic activity.

Moreover, Applicants emphasize that the vast majority of HPV-infected patients develop antibodies to the external L1 papillomavirus protein as they become infected. *See, e.g.*, Galloway, at the bottom of p. 189. In this regard, using chimeric VLPs for delivering E7 into an HPV-infected patient is likely to at least reduce the E7-mediated cell immune response due to the risk of neutralization by pre-existing anti-L1 antibodies present in HPV-infected patients. In addition, the prevalence of antibodies against some HPV proteins is not representative of the disease state as further explained in Galloway who notes, "several groups have demonstrated that the prevalence of antibodies to the HPV 16 or 18 E7 protein is increased in cases with cervical cancer compared with age-matched controls." *See* p. 189, first paragraph, second column. Thus, development of a humoral (antibody-based) immune response in HPV-infected patients as demonstrated by Lowy's chimeric VLPs, may not correlated with a protective anti-tumoral effect.

Thus, Applicants respectfully submit that there is no motivation in the art to choose a mixture of HPV polypeptides produced independently from each other (i.e., in a non-fused manner) when the cited prior art documents disclose the insertion of the sequences encoding the early HPV polypeptides into the coding sequence of the late L2 polypeptide, in order to improve the accessibility to the host's immune machinery. Further, there is no expectation of success that administration of early polypeptides that are not fused to late HPV polypeptides would properly be presented to the host's immune system and confer anti-tumoral (therapeutic) activity.

Withdrawal of this rejection is respectfully requested.

Claims 91, 98, 101-107, and 122 stand rejected under 35 U.S.C. § 103(a) as purportedly obvious over Lowy et al. in view of Galloway, Bubenik et al. (*Intl. J. of Oncol.* 8:477-481 (1996)), Crook et al., and Munger et al. The Examiner argues that one skilled in the art would have been motivated to incorporate IL-2 of Bubenik et al. into a composition comprising the prophylactic L1 and L2 proteins of Lowy et al. and Galloway and the therapeutic proteins taught by Galloway to augment the immune response to the papillomavirus polypeptides. By the present amendment, Claims 91, 98, 101-104, 106, and 122 have been deleted. This rejection, to the extent that it may apply to the method of newly amended independent Claims 105 and 107, is respectfully traversed.

As discussed above, neither Lowy nor Galloway disclose or suggest the use of a polypeptide composition comprising independent (*i.e.*, non-fused) E6, E7, L1, and L2 papillomavirus polypeptides. Concerning the immunostimulatory polypeptide, Lowy et al. disclose the possibility of including additional partners such as a co-stimulatory polypeptide (B7) in the VLP structure, but again teach presentation at the

surface of the VLP through fusion with one of the VLP components. The data of Example 14 identify the BPV L2 region comprised between residues 44-173 as suitable to fuse such a polypeptide. The presently claimed method, in contrast, requires the non-fused status of IL-2 (*i.e.*, expressed from independent expression control elements).

Bubenik et al. disclose a therapeutic strategy that involves administration of HPV-16-infected tumor cells and repeated injection of recombinant IL-2. The animals vaccinated with irradiated cells plus IL-2 were protected to a greater extent than animals only treated with irradiated cells. Applicants draw the Examiner's attention to the immunizing protocol described in the Materials and Methods section (*see, e.g.*, at the top of the second column on p. 478), and particularly to the fact that experimental hamsters were immunized twice with irradiated HPV-16-induced tumor cells and injected in addition twice a day with a dose of 5×10^4 i.u. of recombinant IL-2 for 5 days following each immunization (days 3-7 and 38-42). In other words, the immunized animals received a total of two doses of immunizing irradiated cells and twenty injections of recombinant IL-2 before being challenged with tumor cells on day 56. Bubenik et al. do not disclose or suggest a method as claimed in the presently claimed invention based on the direct administration of a mixture of L1, L2, E6, and E7 papillomavirus polypeptides and IL-2 but rather rely on separate administrations between the immunogen composition (*i.e.*, irradiated tumor cells) and IL-2. It should also be stressed that the quantity of recombinant IL-2 used by Bubenik et al. to obtain an adjuvanting effect is very important. Specifically, 20 injections of IL-2 doses (twice daily over two periods of 5 days) must be performed following the two injections of the vaccinating irradiated tumoral cells. Thus, the strategy of Bubenik et al. is likely to be difficult to implement in human cancer

therapy compared to the method of the presently claimed invention. In addition, due to the huge quantity of IL-2 that is necessary to augment the immune response to HPV-16-infected cells, the Bubenik et al. approach fails to provide a reasonable expectation of success to one of ordinary skill in the art with respect to the direct administration of a mixture of L1, L2, E6, and E7 papillomavirus polypeptides and IL-2.

Accordingly, Applicants respectfully submit that one of skill in the art would not have been motivated to treat papillomavirus-induced dysplasia or cervical cancers by administering the recited papillomavirus polypeptides and IL-2 in light of Bubenik et al., who disclose a cellular approach (administration of irradiated tumor cells) and separate and repeated administration of IL-2 (20 injections). Withdrawal of this rejection is respectfully requested.

Claims 108-110, 113-120, and 123 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Galloway, Bubenik et al., Crook et al., and Munger et al. By the present amendment, Claims 108-110, 113-116, 119, 120, and 123 have been deleted, thereby mooting this rejection as it may apply to these claims. This rejection, to the extent that it may apply to newly amended independent Claims 117 and 118, is respectfully traversed.

Galloway reviews of series of therapeutic vaccinations based upon administration of individual early papillomavirus polypeptides (*see, e.g.*, p. 191), using a cellular approach (*i.e.*, inoculation of fibroblasts expressing either HPV-16 E6 or E7; inoculated mice could reject challenge by a melanoma cell line expressing the HPV oncogenes), a peptidic approach (*i.e.*, a peptide from HPV-16 E7 was found to protect mice from a syngeneic HPV-16 tumor in an MHC-restricted fashion), and

finally, a gene transfer approach (*i.e.*, vaccinia virus recombinants expressing the BPV E5, E6, or E7 genes could retard the development of a BPV-transformed cell line in syngeneic rats).

Galloway does not disclose or suggest, nor motivate one skilled in the art to use the presently recited composition, *i.e.*, a combination of E6 and E7 papillomavirus polypeptides. Further, Galloway fails to disclose or suggest the use of IL-2. Bubenik et al. disclose a therapeutic strategy that involves administration of HPV-16-infected tumor cells followed by repeated injection of recombinant IL-2.

Accordingly, one skilled in the art would not have been motivated to treat papillomavirus-induced dysplasia or cervical cancer by administering E6 and E7 papillomavirus polypeptides and IL-2 in light of Galloway disclose the use of individual early papillomavirus polypeptides and further in view of Bubenik et al. disclosing a cellular therapy requiring the administration of irradiated tumor cells and numerous injections of IL-2.

Applicants respectfully submit that none of the cited publications, either alone or in combination teach or suggest the presently claimed invention. Withdrawal of this rejection is respectfully requested.

Conclusions

From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

If there are any questions concerning this amendment, or the application in general, the Examiner is respectfully requested to telephone Applicant's undersigned representative so that prosecution may be expedited.

Respectfully submitted,

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